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ABSTRACT

Objectives: The aim of this study was to investigate the potential association between occupational exposure to solvents, metals and/or welding fumes and risk of developing Parkinson's disease (PD).
Methods: Data of a hospital based case-control study including 444 PD patients and 876 age and sex matched controls was used. Occupational histories and lifestyle information of cases and controls were collected in a structured telephone interview. Exposures to aromatic solvents, chlorinated solvents and metals were estimated by linking the ALOHA+ job-exposure matrix to the occupational histories. Exposure to welding fumes was estimated using self-reported information on welding activities.
Results: No statistically significant associations with any of the studied metal and solvent exposures were found. However, for self-reported welding activities we observed non-statistically significant reduced risk estimates (third tertile cumulative exposure: OR = 0.51 (95% CI: 0.21–1.24)).
Conclusions: The results of our study did not provide support for an increased chance on developing PD after occupational exposure to aromatic solvents, chlorinated solvents or exposure to metals. The results showed reduced risk estimates for welding, which is in line with previous research, but no clear explanation for these findings is available.

1. Introduction

Various occupational exposures may increase the risk of developing Parkinson's disease (PD) [1]. Exposure to pesticides received much attention, while exposure to organic solvents and (heavy) metals has been studied less.

Organic solvents are widely used in industry and are present in products as fuels, paints, printing inks, degreasers and cleaning products [2]. Because of known neurotoxic effects after acute solvent exposure, concerns have been raised that long term exposures might be associated with neurodegenerative diseases, such as PD [2]. Previous epidemiological studies that have tried to elucidate the potential association of solvent exposure with PD have produced mixed results: two recent literature reviews reported either no or weak effects [3,4]. Most of the studies evaluated solvent exposure in general, but few evaluated risks of classes of solvents or specific solvents. Stronger associations of PD with exposure to specific chlorinated organic solvents were observed in a twin study [5], suggesting that studying specific categories of solvents may be important.

Exposure to metals like manganese, copper, lead, mercury or iron can occur at workplaces in primary metal production or in jobs involving metal working activities like welding, galvanizing, or grinding. The evidence from epidemiological studies that investigated associations of PD with exposure to metals is limited and largely inconclusive [1]. Although clinically distinct from PD, a neurological syndrome with parkinsonian symptoms induced by high occupational exposure to the metal manganese has been

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described [6], and a possible association of PD with chronic exposure to lower levels of manganese has been proposed [7]. Since welding fumes may contain low levels of manganese, welding has been implicated as a potential risk factor for PD, but so far, studies were inconclusive and a meta-analysis showed a decreased risk on PD for welders [8].

We set out to study occupational exposures previously hypothesized to be related to PD, including metals, welding fumes and categories of organic solvents, specifically aromatic and chlorinated solvents, and risk of PD in a large PD case-control studies in the Netherlands.

2. Methods

2.1. Cases and controls

Details about the study design were described previously [9]. Briefly, cases and controls were recruited between April 2010 and June 2012 from 5 hospitals in the Netherlands. Eligible patients were diagnosed with Parkinson's disease in one of the participating hospitals between January 2006 and December 2011. Subjects initially diagnosed elsewhere and referred to one of the participating centers for follow-up care or second opinion were excluded. Since in the Netherlands all PD patients are seen in a hospital-based clinic, included PD patients could therefore be regarded to be representative for all PD patients in the service areas of the 5 participating hospitals. For each case, two matched controls were selected from persons that were seen at the department of neurology for non-neurodegenerative complaints (median nerve neuropathy; ICD-10 G56.0 and G56.1, ulnar nerve neuropathy; ICD-10 G56.2, thoracic and lumbar disc disease; ICD 10 G55.1, G54.3 and G54.4, and sciatica; ICD-10 M54.3 and M54.4). The controls were matched to the cases on hospital, visiting date (within 3 years of the cases diagnose year), sex and age (interquartile range age difference: 6–33 days). At recruitment 93% of the eligible patients were still alive and a total of 448 PD patients participated. The participation rate was 45% for cases and 35% for controls. For 12 cases only 1 suitable control was found and for 4 cases no controls were found, leaving 444 PD patients and 876 controls who were included in the analyses. The study was approved by the Medical Ethics Committee of St Elisabeth Hospital Tilburg, the Netherlands, and all participants provided their informed consent.

2.2. Data collection

Participants were interviewed in a standardized computer-assisted telephone interview by one of three trained interviewers. During the interview, the complete residential and occupational history was obtained, as were questions about electrical welding activities, anthropometric measures, selected dietary items, smoking and a medical history. All jobs a participant had performed for at least 6 months were included in the occupational history. The study participants were asked to report on number of years and hours per week worked, job title, type of industry, company name and main tasks of participant. When a participant reported electrical welding activities during a job, questions about type of electrical welding, frequency (<1/year, <1/month, 1–3/month, 1–3/week, >3/week) and duration were asked. Furthermore, questions about years and frequency of non-work related electrical welding activities were asked. All jobs were coded according to the International Standard Classification of Occupations 1968 (ISCO68) and 1988 (ISCO88).

2.3. Exposure assessment

All ISCO88 job codes were linked to the ALOHA+ job-exposure matrix (JEM) [10]. This JEM assigns exposure to chlorinated solvents, aromatic solvents and metals as no, low or high using arbitrary weights for intensity and probability of exposure of 0, 1 and 4 respectively. Exposure to welding fumes from electrical welding was assigned when a participant reported to have been welding at least weekly in a particular job. An exposure score of 1 (low) when a participant welded frequently (1–3 days per week) and an exposure score of 4 (high) was assigned when welding was part of day-to-day work (4 or more days per week). Participants also received an exposure score of 1 (low) for each year with more than 50 days of non-work related welding. Duration of exposure to metals, solvents or welding fumes was defined as number of years with low or high exposure. Cumulative exposure was calculated by summing the exposure score (0, 1 or 4) for all years until the year prior to diagnosis.

2.4. Statistical analysis

Odds ratios and 95% confidence intervals were estimated using conditional logistic regression. The exposed subjects were categorized in three groups based on tertiles of the distributions of exposure among controls. Variables included in the adjusted analyses were total pack-years of smoking (5 categories), total coffee consumption (4 categories) and occupational skill and status (4 categories): All jobs in the occupational histories were divided according to major ISCO88 groups (first digit), 1–3: high-skilled white-collar worker, 4–5: low-skilled white-collar worker, 6–7: high-skilled blue-collar worker and 8–9: low-skilled blue-collar worker. Participants were subsequently categorized according to occupational skill and status based on the job category in which a participant had worked most years.

3. Results

Table 1 shows the general characteristics of cases and controls. Mean age of the cases was 68 years with 63.3% of the cases being men. Cases smoked on average fewer cigarettes, drank less coffee and were more often high-skilled white-collar workers than controls.

The results for occupational exposure to aromatic and chlorinated solvent are presented in Table 2. Cumulative exposure to aromatic and chlorinated solvents was moderately correlated (Pearson correlation coefficient: 0.41). For both classes of solvents, slightly more controls than cases ever had a job with high exposure. No significant associations were observed, however, somewhat more cases than controls had their exposure to aromatic solvents in the highest tertile for both duration and cumulative exposure, resulting in non-statistically significant elevated odds ratios. For exposure to chlorinated solvents, a non-significant elevated odds ratio was seen for individuals in the highest tertile of duration, but not for cumulative exposure. The majority of individuals exposed to solvents were men: 82% for aromatic solvents and 88% for chlorinated solvents. Stratified analyses by gender showed similar results for women and men for both types of solvents, but given the low number of occupationally exposed women, risk estimates were imprecise (data not shown).

Exposure to metals also occurred slightly more frequently in controls than in cases (see Table 3). The analyses on duration and cumulative exposure did not provide evidence for an increased risk of PD in persons occupationally exposed to metals. There were only 16 women with exposure to metals. Similar as the other exposures more controls than cases reported to have ever had a job involving more than 3 days per week of electrical welding (high exposure), resulting in a significant decreased odds ratio (see Table 3). The analyses that were adjusted for potential confounders and analyses on duration and cumulative welding exposure no longer showed statistically significant reduced odds ratios. Only 2 women reported welding on a weekly basis.

4. Discussion

Our study did not provide support for an increased risk of Parkinson's disease among persons occupationally exposed to aromatic solvents, chlorinated solvents or metals. For self-reported electrical welding activities we observed reduced odds ratios.

Strengths of our study were the use of full occupational histories in combination with a JEM to objectively estimate life-time occupational exposures, because reporting occupational histories is less influenced by a potential recall bias than self-reported use of substances or exposures. Furthermore, instead of using a single category of solvent exposure, we studied two classes of organic solvents: aromatic and chlorinated solvents separately. In addition, we had detailed information on lifestyle factors most notably detailed information on smoking which in line with a range of previous reports [11], showed a reduced risk of PD in smokers.

However, a limitation of the use of JEMs is that the same exposure level is applied to all jobs with the same job-title, resulting most likely in non-differential misclassification of exposure and consequently attenuation of study results.

Another limitation of the study include the low participation rate potentially hampering generalizability of results. Participation rate was higher among subjects below 70 (participation cases: 66%, controls: 39%) and therefore we repeated the analyses on participants age 70 or younger. Results did not materially change (data not

Table 1
General characteristics of cases and controls.

	Cases (n = 444)	Controls (n = 876)
Men, No (%)	281 (63.3%)	557 (63.6%)
Age at interview, median (range)	68 (34–91)	68 (34–90)
Age at diagnosis, median (range)	67 (34–90)	–
Cigarette smoking[a]		
Never smoked, No (%)	207 (46.6%)	243 (27.7%)
>0–7.8 pack-years, No (%)	86 (19.4%)	161 (18.4%)
>7.8–17.5 pack-years, No (%)	67 (15.1%)	155 (17.7%)
>17.5–29.4 pack-years, No (%)	45 (10.1%)	160 (18.3%)
>29.4–103 pack-years, No (%)	39 (8.8%)	157 (17.9%)
Coffee consumption[b]		
0–97 consumption-years, No (%)	128 (28.8%)	220 (25.1)
>97–156 consumption-years, No (%)	146 (32.9%)	221 (25.3)
>156–214 consumption-years, No (%)	90 (20.3%)	216 (24.7)
>214–720 consumption-years, No (%)	80 (18.0%)	218 (24.9)
Occupational skill and status[c]		
High-skilled white-collar worker, No. (%)	198 (44%)	335 (38%)
Low-skilled white-collar worker, No. (%)	87 (20%)	187 (21%)
High-skilled blue-collar worker, No. (%)	101 (23%)	202 (23%)
Low-skilled blue-collar worker, No. (%)	58 (13%)	152 (17%)

[a] Pack-years of cigarette smoking was calculated by dividing average number of cigarettes per day by 20 multiplied by the number of years of smoking. Ever smokers were divided based on the quartiles of the exposure distribution among the controls. Never smokers constitute a separate category.

[b] Consumption-years were calculated by multiplying the average amount of coffee consumptions per day with the estimated number of years of coffee consumption. The participants were divided based on the quartiles of the exposure distribution among the controls. The number of never coffee drinkers was too low (3%) to be analyzed as a separate group. Coffee consumption information was missing for one control.

[c] The categories of occupational skill and status were made according to major ISCO groups (first digit of the ISCO 88 job codes). 1–3: High-skilled white-collar jobs, 4–5: Low-skilled white-collar jobs, 6–7: High-skilled blue-collar jobs, and 8–9: Low-skilled blue-collar jobs. The participants were categorized according to the group in which they had worked most years during their career.

shown). In addition, sensitivity analyses were performed leaving out one of the 4 non-neurodegenerative complaints subgroups of controls at a time. This did not materially affect the reported odds ratios (data not shown), suggesting that our results were not influenced by characteristics of one of the neurological conditions included in the control group.

Because sometimes the initial PD diagnosis changes as disease progresses, the use of recently diagnosed patients may have

Table 2
Parkinson's disease and exposure to aromatic and chlorinated solvents as assessed by a job-exposure matrix: conditional logistic regression analyses.

	Cases *n* (%)	Controls *n* (%)	Crude OR (95% CI)	Adjusted[c] OR (95% CI)
Aromatic solvents (JEM)				
Never	262 (59.0)	505 (57.6)	1	1
Ever exposure				
low	168 (37.8)	323 (36.9)	0.99(0.77–1.27)	0.97(0.73–1.29)
high	14 (3.2)	48 (5.5)	0.56(0.30–1.03)	0.82(0.43–1.58)
Duration[a]				
1–7	57 (12.8)	132 (15.1)	0.84(0.59–1.18)	0.88(0.61–1.26)
8–24	54 (12.2)	117 (13.4)	0.90(0.63–1.30)	0.91(0.62–1.34)
25–67	71 (16.0)	122 (13.9)	1.13(0.80–1.61)	1.26(0.80–1.97)
Cumulative exposure[b]				
1–8	58 (13.1)	130 (14.8)	0.86(0.61–1.21)	0.89(0.61–1.28)
9–27	52 (11.7)	119 (13.6)	0.86(0.60–1.24)	0.86(0.58–1.27)
28–192	72 (16.2)	122 (13.9)	1.14(0.80–1.62)	1.33(0.86–2.05)
Chlorinated solvents (JEM)				
Never	336 (75.7)	645 (73.6)	1	1
Ever exposure				
low	71 (16.0)	141 (16.1)	0.96(0.70–1.31)	1.04(0.74–1.46)
high	37 (8.3)	90 (10.2)	0.78(0.52–1.18)	0.86(0.55–1.36)
Duration[a]				
1–8	26 (5.9)	85 (9.7)	0.59(0.37–0.94)	0.65(0.40–1.06)
9–24	38 (8.6)	74 (8.4)	0.98(0.65–1.49)	1.01(0.65–1.57)
25–50	44 (9.9)	72 (8.2)	1.10(0.77–1.74)	1.39(0.88–2.20)
Cumulative exposure[b]				
1–11	27 (6.1)	78 (8.9)	0.67(0.43–1.06)	0.74(0.46–1.19)
12–37	43 (9.7)	78 (8.9)	1.05(0.70–1.58)	1.09(0.70–1.69)
38–180	38 (8.6)	75 (8.6)	0.98(0.64–1.49)	1.15(0.72–1.84)

[a] Duration of exposure was defined as all years in the job history with low or high exposure. Exposed were divided based on the tertiles of the exposure distribution among the controls.

[b] Cumulative exposure was calculated summing exposure of all years in the job history using weights (0 for no, 1 for low and 4 for high exposure). Exposed were divided based on the tertiles of the exposure distribution among the controls.

[c] The adjusted model includes cigarette smoking (5 categories), coffee consumption (4 categories) and occupational skill and status (4 categories). Because information on coffee consumption was missing for 1 participant, this participant was excluded from adjusted analyses.

Table 3
Parkinson's disease and exposure to metals as assessed by a job-exposure matrix and self-reported welding: conditional logistic regression analyses.

	Cases *n* (%)	Controls *n* (%)	Crude OR (95% CI)	Adjusted[c] OR (95% CI)
Metals (JEM)				
never	348 (78.4)	671 (76.6)	1	1
Ever exposure				
Low	51 (11.5)	99 (11.3)	0.98(0.68–1.42)	1.06(0.72–1.58)
High	45 (10.1)	106 (12.1)	0.81(0.55–1.19)	0.88(0.58–1.33)
Duration[a]				
1–8	31 (7.0)	69 (7.9)	0.86(0.56–1.33)	1.03(0.64–1.65)
9–23	25 (5.6)	69 (7.9)	0.70(0.44–1.13)	0.69(0.42–1.15)
24–53	40 (9.0)	67 (7.6)	1.15(0.75–1.76)	1.27(0.78–2.05)
Cumulative exposure[b]				
1–14	32 (7.2)	68 (7.8)	0.90(0.58–1.34)	0.98(0.62–1.56)
15–44	32 (7.2)	71 (8.1)	0.87(0.55–1.36)	0.93(0.57–1.52)
45–180	32 (7.2)	66 (7.5)	0.93(0.59–1.46)	1.00(0.61–1.64)
Welding (Self-Report)				
Never	419 (94.4)	803 (91.7)	1	1
Ever exposure				
Low	19 (4.3)	44 (5.0)	0.84(0.49–1.45)	0.93(0.53–1.68)
high	6 (1.4)	29 (3.3)	0.41(0.17–0.99)	0.41(0.16–1.01)
Duration[a]				
1–7	10 (2.3)	26 (3.0)	0.75(0.35–1.58)	0.82(0.38–1.78)
8–31	5 (1.1)	23 (2.6)	0.43(0.16–1.13)	0.45(0.16–1.25)
32–50	10 (2.3)	24 (2.7)	0.82(0.39–1.71)	0.85(0.39–1.86)
Cumulative exposure[b]				
1–13	11 (2.5)	26 (3.0)	0.83(0.40–1.71)	0.92(0.43–1.96)
14–40	7 (1.6)	23 (2.6)	0.60(0.26–1.40)	0.73(0.30–1.80)
41–200	7 (1.6)	24 (2.7)	0.57(0.25–1.33)	0.51(0.21–1.24)

[a] Duration of exposure was defined as all years in the job history with low or high exposure. Exposed were divided based on the tertiles of the exposure distribution among the controls.
[b] Cumulative exposure was calculated summing exposure of all years in the job history using weights (0 for no, 1 for low and 4 for high exposure). Exposed were divided based on the tertiles of the exposure distribution among the controls.
[c] The adjusted model includes cigarette smoking (5 categories), coffee consumption (4 categories) and occupational skill and status (4 categories). Because information on coffee consumption was missing for 1 participant, this participant was excluded from adjusted analyses.

resulted in included cases that do not have PD. However, as at least 80% of the participants have a true PD pathology [12], and as misclassification of disease status would likely have been non-differential by exposure it is unlikely to have resulted in biased risk estimates.

Recent reviews on solvent exposure and PD risk showed that observed risk estimates of most previous studies were between 1.0 and 1.5, suggesting that a weak association might exist [3,4]. We only observed statistically non-significant slightly elevated odds ratios for the highest tertile of duration and cumulative exposure for aromatic solvents. No increased risks were observed for cumulative exposure to chlorinated solvents, which is in contrast to a previous study that found strong positive associations for several chlorinated solvents (trichloroethylene, perchloroethylene and carbon tetrachloride) [5]. Because these solvents are among the most commonly used chlorinated solvents, it is unlikely that differences in risk estimates from their and our study are caused by the fact that we grouped all chlorinated solvents together. As such the difference between the studies remains unknown.

The result of our analysis on occupational exposure to metals is in line with previous studies that analyzed occupational metal exposure as a single entity and observed no or only slightly increased risks of PD [13–17]. Unfortunately, we were not able to analyze specific metals separately. Potential existing effects of single metals may therefore be diluted in the results, especially if the prevalence of exposure to a specific metal is low.

As another proxy for exposure to metals, we also evaluated the self-reported frequency of welding per week as welding fumes contain manganese and other metals. We did not observe higher risks in persons classified to have experienced higher levels of cumulative exposure, but instead, reduced odds ratios for frequent welders were observed. Only questions on electrical welding methods were included in the telephone interview because they were originally intended for estimating electromagnetic field exposure. However, because electrical welding constitutes the most frequently used welding application since the second half of last century [18], omitting gas welding is unlikely to have strongly affected our results. Several factors determine exposure levels to manganese or other metals due to welding: exposure levels may increase with higher content in the base metal and welding rods, when electrode current densities and arc time is high, and in rooms with poor ventilation [6]. Unfortunately, information on these determinants was not collected in our study and could therefore not be explored. Of the exposed, 85% reported shielded metal arc welding; limiting our abilities to perform meaningful analyses stratified by type of electrical welding.

Although our finding of decreased odds ratios among the most frequent welders might be a chance finding related to the low number of exposed which resulted in wide confidence intervals, the finding is consistent with a recent meta-analysis showing a summary risk ratio of 0.86 (95% CI 0.80–0.92) for PD in welders [8]. Explanations brought forward for the risk estimates below unity include subtle, sub-clinical effects that appear long before diagnosis and that might lead to a self-selection of affected persons into specific jobs [16]. The time interval between onset of motor symptoms and diagnosis is around one to two years [19,20]. Non-motor preclinical manifestations (e.g. constipation) of PD may occur much earlier, where time frames between a few years and more than two decades prior to diagnosis have been described [21]. However, because onset of PD is late in life, this means that in order to fully explain the reduced risk estimates, such non-motor manifestations would have to appear much earlier than previously reported and to have a relatively strong impact on career-choices, which appears unlikely. Also, it has been hypothesized that a premorbid parkinsonian personality predispose cases to select for white collar jobs associated with low exposures, such as teaching or

legal professions, but no clear evidence exists to that effect [19,22]. Further possible explanations for the decreased odds ratios include protective effects of physical activity [23] or smoking [24] which both occur more frequently in jobs with relatively high exposure to solvents, metals or welding. We adjusted our results for smoking behavior and for skill and status of jobs using a relatively crude categorization based on major ISCO88 groups. This generally led to odds ratios closer to unity, but residual confounding by those factors cannot be ruled out.

In conclusion, the results of our hospital based case-control study did not provide support for an association between PD risk and occupational exposure to chlorinated or aromatic solvents. However, the slightly elevated odds ratios for the highest exposure categories for aromatic solvents are in line with previous reports that an association between solvents and PD risk may exist. Our results did not provide any evidence for an increase in PD risk after exposure to metals. However, we did observe, similarly as others, reduced risk estimations for the association between exposure to welding fumes and PD risk. A biological mechanism for this later observation is however missing and therefore should be interpreted with caution.

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